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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kaumaya *et al.*

Application No.: 09/990,574

Filed: November 21, 2001

For: Agents for Blocking T Cell Mediated Immune Reactions

Group Art Unit: 1644

Examiner: Ilia I. Ouspenski

Attorney Docket No.: 18525/04028

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DECLARATION UNDER 37 C.F.R. §1.132

I, Pravin T. P. Kaumaya, state as follows:

1) I am a co-inventor of the above-captioned patent application.

2) I am a co-author of Srinivasan et al., "A CD28 CDR3 peptide analog inhibits CD4+ T-cell proliferation *in vivo*," in Peptides for the New Millennium (1999), pp. 689-690.

3) On March 25, 1999, I submitted an abstract to the 16th American Peptide Symposium organizers, which was published in the Abstract book for the Symposium on June 26, 1999. A copy of the Abstract submitted to that Symposium is attached hereto.

4) The Abstract mentions a retro inverso peptide analog, but does not disclose its actual sequence.

5) A poster presentation was made at the Symposium, but the content of the poster presentation did not extend beyond what is shown in Srinivasan et al. or the submitted Abstract.

6) Members of my laboratory attended the Symposium and a graduate student from my laboratory, Mythily Srinivasan, made the poster presentation.

7) I specifically instructed Ms. Srinivasan not to discuss the sequence of the retro inverso peptide analog, as I was contemplating patent protection at that time. In a telephone conversation in November 2005, Ms. Srinivasan reassured me that the sequence had not been disclosed.

8) The sequence of the retro inverso peptide analog was not disclosed orally at the Symposium.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

11/30/05 _____

Date

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Pravin T.P. Kaumaya

A CD28-CDR3 PEPTIDE ANALOG TO INHIBIT T CELL RESPONSES IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS.

Mythily Srinivasan,[1] Richard M. Wardrop,[2] Caroline C. Whitacre,[2] Pravin T. Kaumaya,[1] from [1]Department of Obstetrics and Gynecology and [2]Department of Medical Microbiology and Immunology Ohio State University, Columbus, Ohio 43210.

Multiple sclerosis (MS), a human demyelinating disease involves a T cell response against central nervous system myelin antigens. Experimental autoimmune encephalomyelitis (EAE) is an animal model that shares clinical, histopathological and immunological features with MS. Following binding of the encephalitogenic peptide to MHC Cl II by the peptide specific T cell receptor, the antigen presenting cells upregulate the expression of oligomerized B7 ligands and the T cells upregulate the expression of CD28 inducing T cell proliferation. Activated T cells later express CTLA-4, a homologue of CD28 and a negative regulator of T cell response. Thus the B7/CD28: CTLA-4 costimulatory system plays a critical role in activation vs down-regulation of the immune response and is a highly promising therapeutic target for regulating autoimmune diseases.By interfering with this interaction, modulation of T cell responses are restricted to the T cells whose receptors are engaged. The goal of the present study is to overcome the problem of proteolytic degradation while retaining the selected receptor antagonist activity. We synthesized a retro inverso peptide analog of the parent ligand binding epitope of the CD28 extracellular cellular domain as the alternate peptide receptor (APR) for B7 ligands. The end groups of the CD28 APR peptide were blocked to mimic parent receptor-ligand interaction. The CD28 APR competes with the ECD of CD28 for binding sites on B-7 molecules providing steric hindrance. The addition of synthetic CD28 APR inhibited proliferation of CD4+ T cells from lymph nodes and spleens of mice transgenic for the T cell receptor that recognizes the myelin basic protein (MBP). Nearly 70% inhibition was observed with the addition of 50μM CD28 APR. The secretion of the proinflammatory cytokine IL-2 was decreased with the addition of CD28 APR, as observed by the Elisa spot assay. The mechanism of action of CD28 APR is being characterized.